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A CASE OF TOXIC AMBLYOPIA,

WITH AUTOPSY AND MICROSCOPICAL EXAMINATION OF THE SPECIMENS.[1]

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of Philadelphia.

Although von Graefe, Leber, and Förster surmised that central scotoma was, under certain circumstances, a symptom of lesion of the optic nerve, absolute proof of this belief was not reached until 1880, when Samelsohn published his researches on the pathological anatomy of retrobulbar neuritis (central amblyopia). True, some earlier observations (Erisman, in 1867, and Leber, in 1869) are on record, but, as Uhthoff has observed, their cases were not pure examples of intoxication-amblyopia, and, therefore, Samelsohn has the credit of publishing the first well-studied case of this affection which came to autopsy. Since the date of this paper the literature has been enriched by the description of about twenty additional post-mortem and microscopical examinations of intoxication-amblyopias; but even now there is not perfect accord with reference to the exact pathological anatomy of this interesting affection, and hence no excuse seems necessary for the record of a new case.[2] It is as follows:

M. T., aged sixty years, born in Ireland, widower, a messenger in the Philadelphia Hospital, consulted me first in the spring of 1895, with the hope of obtaining relief for failing vision.

History. With the exception of frequent attacks of facial neuralgia,

[1] Read before the American Ophthalmological Society, in Washington, May, 1897.

[2] In the following list are the references to the most important papers describing the lesions in intoxication-amblyopias based upon microscopical examination:

1. Samelsohn: Graefe's Archiv, 1882, xxviii., Abth. 1, pp. 1–110.
2. Vossius: Ibid., xxviii., Abth. iii. p. 201.
3. Nettleship and Edmunds: Trans. Ophth. Soc. of the U. K., 1881, i. p. 124.
4. Bunge: Ueber die Gesichtsfeld und Faserverlauf im Optischen Leitungs-Apparat. Halle, 1884.
5. Thomsen: Archiv f. Psychiatrie, xiii. p. 352.
6. Uhthoff: Graefe's Archiv, 1886, xxxii., Abth. iv. 95–108, and ibid., xxxiii., i. pp. 257–318.
7. Wildbrand: Bericht über die Versammlung der Ophthalmolog. Gesellschaft, xxii., Heidelberg, 1892, p. 84.
8. Sachs: Archives of Ophthalmology, 1889, xviii., No. 2, pp. 133–162, and ibid., 1894, xxiii., No. 4, pp. 226–444.
9. Stöltzing: Klinische und Anatomische Beiträge zur Intoxications-amblyopie, Inaug. Dissert., Marburg, 1893. This thesis contains abstracts of all microscopical examinations in cases of toxic amblyopia up to date of its publication.
10. Nuel: Archives d'Ophtalmologie, October, 1895; March and August, 1896.
11. Schmidt-Rimpler: Bericht über die Versammlung der Ophthalmolog. Gesellschaft, xxv., Heidelberg, 1897, p. 99.

In addition to the cases referred to above, fifteen in number, there have been about six others, notably those of Leber, Erisman, Magnan, and Bidecker. Schmidt-Rimpler's paper describes especially diabetic amblyopia.

the patient had been for many years a reasonably healthy man. He had been an inmate of the hospital for thirteen years, during the last nine of which he had been employed as a messenger in the Training School. According to the rules of the institution, once in two months he was given leave of absence lasting twenty-four hours. He always returned on time, and although it is probable he was not an abstainer during these holiday hours, he was never known to be intoxicated. While within the walls of the hospital it was not possible for him to obtain liquor. Previous to his entrance into the hospital he kept a saloon, and no doubt drank liquor, but there is no history of alcoholic excesses. For a number of years he had smoked excessively; indeed, he was seldom without a pipe in his mouth. He drank tea freely. There was no history of venereal disease and no signs of its influence. For a year before his death there was distinct evidence of physical failure. He suffered much from headache, and the urine was known to contain albumin. The vision of each eye had been poor for some months before he reported for treatment, and he was driven to seek advice because of his inability to read the newspaper.

Examination. The patient was a tall, well-preserved, and, at that time, an apparently healthy man. His radial and temporal arteries were rather hard, and the pulse showed high tension. The urine was not examined on this date, but subsequently—*i. e.*, about eighteen months later—it was found to contain albumin and casts. Sugar was not present.

Eyes. V. of R. E. equalled 5/60, and was unimproved by a glass. The ophthalmoscope revealed H. of 2 D., a vertically oval, rather pallid disk, the temporal side being paler than the general surface. The vessels were of normal size; there were no retinal or choroidal lesions. The nucleus of the crystalline lens was hazy. The peripheral form-field was normal, but there was a central scotoma for red and green. The pupil-reactions were normal.

V. of L. E. equalled 5/40, unimproved by a glass, and ophthalmoscopically the same conditions were present as those on the right side. The form-field was normal and there was a central color-scotoma, somewhat smaller than on the right side. The lens was hazy; the pupil normal.

The patient was advised to discontinue the use of tobacco, and was ordered strychnine. It is probable that he tried to follow this advice, but with indifferent success, and practically he did not stop the use of tobacco until his final illness. His eyes were examined from time to time, and the conditions already described remained unaltered.

The fields of vision in the early fall of 1896 are represented in the accompanying diagrams, viz.: O. D. a normal form-field, contracted blue and red fields, loss of the perception of green, and a large central scotoma extending somewhat beyond the limits usually seen in the earlier stages of intoxication-amblyopia, and probably reaching the limit of the red field above; O. S. a normal form-field, moderate contraction of the blue and red fields, green blindness, and a typical central scotoma, 20 degrees outward, 7 degrees upward, 6 degrees downward, and about 5 degrees inward. (Figs. 1 and 2.)

On December 7, 1896, the patient was taken suddenly ill and rapidly developed pneumonia, with uræmic symptoms. The urine contained albumin and granular and hyaline casts. Stupor supervened, and death occurred on the third day.

The autopsy was made sixteen hours after death. Permission to open

the skull-cap only was obtained, and the posterior halves of the eyes, together with the optic nerves, chiasms, and tracts, were removed and placed in Müller's fluid. With the exception of œdema of the pia-arachnoid there were no abnormalities of the brain or cerebellum. After six weeks' hardening in frequently changed Müller's fluid, kept at a temperature between 60° and 70° F., serial sections of the optic nerves, chiasms, and tracts were cut and stained according to the Weigert and Weigert-Pal methods. Longitudinal sections of the posterior halves of the eyeballs were similarly cut and stained. For the study of the histological details the carmine method was employed. For the preparation of these sections I am greatly indebted to Dr. J. Dutton Steele.

FIG. 1.

Left

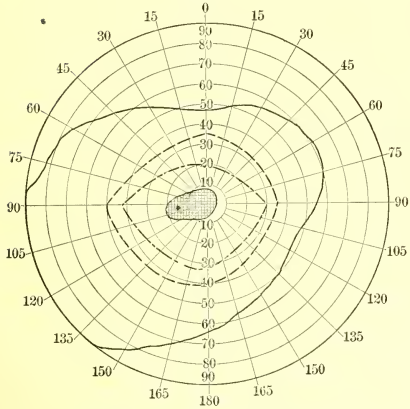
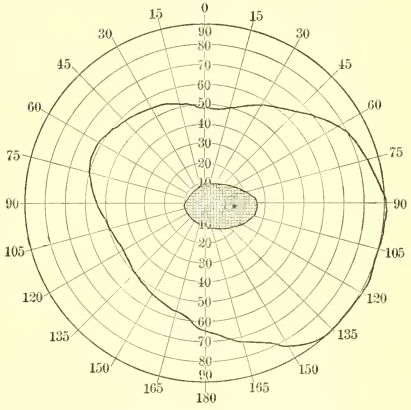


FIG. 2.

Right



The continuous line indicates the limits of the form-field; the broken lines th e color-fields, – – – blue; —·—·— red; the central cross-hatching the scotomas. There was green blindness. It was difficult to ascertain the limits of the color-fields of the right eye; they are, therefore, not represented. The limits of the scotoma were also difficult to determine; they probably reached the boundary of the red field above.

The test-objects were white and colored circles, one cm. in diameter. The scotomas were determined with ¼ cm. square colored tests.

1. *Longitudinal section of the posterior half of the right bulbus and 5 mm. of the optic nerve.* (Weigert and Weigert-Pal stain.) The degenerated area occupies strictly the temporal half of the nerve and passes to the pial sheath. Close to the lamina the degeneration is complete; further onward are traces of normal nerve-fibres. (Fig. 1, Plate I.)

2. *Transverse sections of right nerve 8 mm. behind the globe.* The degenerated patch occupies the temporal (lower and outer) portion of the nerve, forming a somewhat heart-shaped area, extending at one point to the sheath. This area is imperfectly divided by a faint line of partially preserved nerve-fibres. (Fig. 2, Plate I.)

3. *Transverse section of nerve 13 mm. behind the globe.* The degenerated patch, still occupying the lower and outer part of the nerve, becomes more contracted and assumes an oval or somewhat meniscus-like shape. (Fig. 3, Plate I.)

4 and 5. *Transverse section of nerve in the region of the optic foramen.* The degenerated patch tends to leave the periphery and pass to the centre, although still somewhat eccentrically placed. (Fig. 4, Plate I.) Fur-

ther onward it is still more centrally placed, with the broader end toward the outer border. (Fig. 5, Plate I.)

6. *Transverse section of nerve in the intracranial region.* The degenerated patch is somewhat crescentic and with the broader end toward the temporal side. It occupies a position somewhat above the centre of the nerve. (Fig. 5, Plate I.)

1. *Longitudinal section of the posterior half of the left bulbus and 8 mm. of the optic nerve.* (Weigert and Weigert-Pal stain.) The degenerated area again strictly occupies the temporal half of the nerve and passes to the pial sheath. Close to the lamina the degeneration is almost complete. Further toward the brain patches of retained nerve-tissue are seen. If the patch is studied in its relation to the vessels, it is seen in certain sections to occupy a somewhat triangular patch which, in cross-section at this point, would produce the well-known wedge-shaped patch with the apex toward the vessels, which has so often been described. (Fig. 1, Plate II.)

2. *Transverse section of the left nerve 10 mm. behind the globe.* The degenerated patch forms a crescentic or somewhat meniscus-like area with its concavity toward the vessels and reaching at its outer border quite to the pial sheath. It is divided by a distinct line of retained normal nerve-fibres, the line running in the long axis of the patch. (Fig. 2, Plate II.; compare with Fig. 3, Plate I.)

3 and 4. *Transverse sections of the nerves in the neighborhood of the optic foramen.* The degenerated patch again tends to leave the periphery and reach the centre (Fig. 3, Plate II.; compare with Fig. 4, Plate I.), which it more nearly attains at the foramen (Fig. 4, Plate II.; compare with Fig. 5, Plate I.), its broadest end being toward the temporal side. The remainder of the nerve to the chiasm tallies closely with that upon the right side, as does also the appearance of the optic tract. Therefore figures and descriptions need not be reproduced.

5. *Transverse section of the right nerve just in advance of the chiasm.* The section is somewhat broken, but shows the degenerated patch occupying an irregular area in the centre of the section, and reaching below to its margin. (Fig. 5, Plate II.)

6 and 7. *Transverse section of the chiasm and optic tracts.* The degenerated patches occupy symmetrical positions in either end of the ellipse, being nearly centrally placed and gradually narrowing to a point of decussation in the centre of the chiasm. (Fig. 6, Plate II.) In the optic tract the degenerated area at first occupies almost exactly the centre of the tissue, and becomes less and less marked as the connection between this tissue and the mid-brain is being formed. (Fig. 7, Plate II.)

The degeneration has attacked that portion of the optic nerve ordinarily known as the papillo-macular bundle, or the maculary fascicle. It pursues a course similar to the one already described by Samelsohn, Vossius, Uhthoff, and other observers, beginning in a wedge-shaped area of degeneration on the temporal side of the optic nerve, which position it maintains, although in a somewhat altered shape, being at first heart-shaped and later crescentic, for about 10 mm. behind the globe. The area then approaches but never quite reaches the centre of the nerve, and maintains this position until it reaches the foramen. In the intracranial portion of the nerve the patch again becomes distinctly crescentic and occupies a position above the centre. In the chiasm the foci of de-

Plate I.

Fig. 1.

Fig. 2.

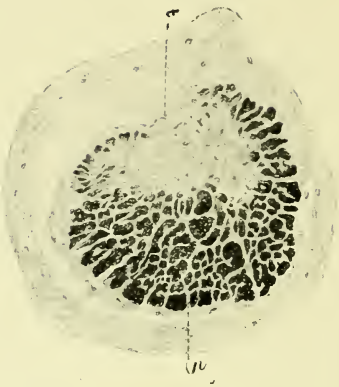


Fig. 3.

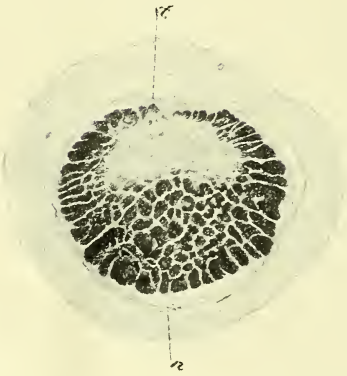


Fig. 4.

Fig. 5.

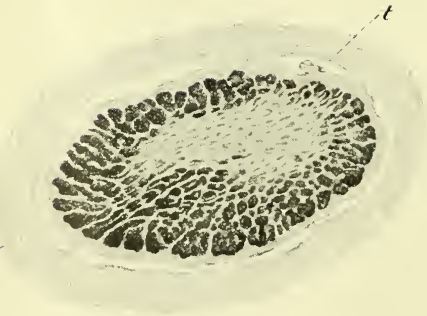


Fig. 6.

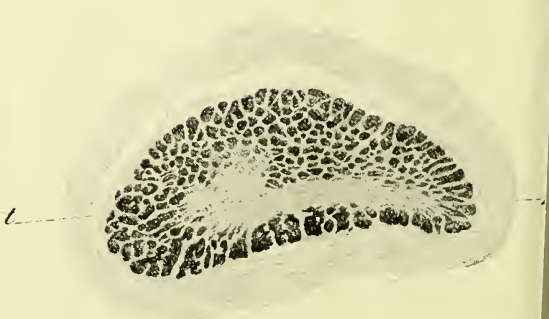


Plate II.

Fig. 1.

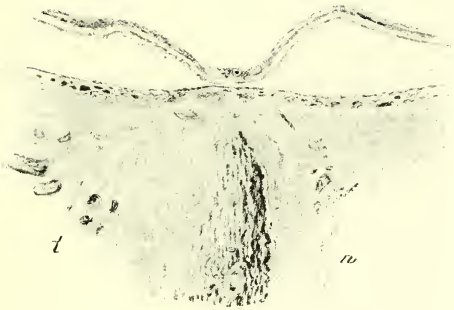


Fig. 2.

Fig. 3.

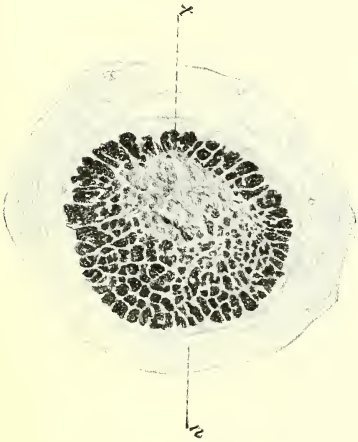


Fig. 4.

Fig. 5.

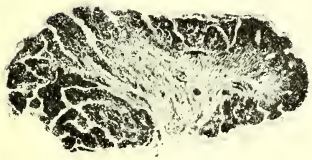


Fig. 7.

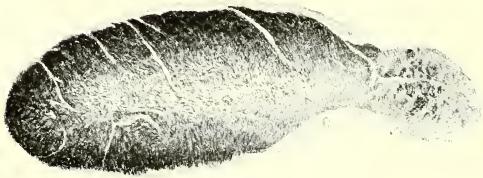


Fig. 6.

generation are symmetrically placed slightly below the centre, while in the tract the position is almost exactly central.

Examination of the diagrams and slides further indicates, first, that the process was more intense and the degeneration more pronounced upon the right side than upon the left side. This corresponds with the visual field examination, which showed a larger scotoma upon the right side and a greater loss of color-perception, with the production of spots of absolute scotoma. Second, that the degeneration both upon the right and left sides is more marked in two situations, namely, just posterior to the lamina cribrosa, and again at the optic foramen, although just before reaching this point there is an area with well-preserved patches of nerves. (See Fig. 4, Plate I.; Fig. 4, Plate II.)

Finer Microscopical Details. 1. *The Retina.* The retinal elements, with the exception of the optic-nerve fibre-layer and the ganglion-cells, may be dismissed at once, because they present no abnormalities of interest in the present discussion. The nerve-layer, especially as the fibres approach the papilla on the side corresponding to the degeneration in the temporal half of the optic nerve, is narrower than normal, although it is to be remembered that the fibre-layer is naturally less developed in the temporal than in the nasal retina. The contraction of this layer under similar circumstances has been noted by Bödecker and other observers.

The *ganglion-cells* are normally placed and are not numerically decreased. Comparing them with those of a retina known to be healthy, they appear in the neighborhood of the nerve-head to be small and the development of their processes imperfect, a phenomenon which has also been observed by Sachs. In the macular zone, however, there is the usual increase in the number of ganglion-cells, which are well constituted, *exhibiting neither atrophy nor degeneration.*

The coats of the *retinal vessels* are greatly thickened, a thickening quite in accord with arterial change elsewhere in the ocular tissues.

2. *The choroid* is practically free from changes, save those referred to in the vessels.

3. *The optic nerves.* The trabeculæ of the laminæ are thickened and compressed, and the vascular septa of nerve (in cross-section) generally thicker than under normal conditions. The nerve-fibres surrounding the patch of diseased tissue, situated as already described, present a normal appearance. As the lesion is approached there are an augmentation of nuclei, a marked thickening of the connective-tissue septa, and a disappearance and degeneration of the nerve-fibres. The diseased patch is sharply separated from its normal surroundings.

4. *The vascular changes* have been described in general terms. In particular it may be said that the small nutrient vessels of the optic nerve are greatly thickened—so greatly that in many places they are practically converted into small fibrous cords. The same changes are manifest in

the walls of the major vessels, and, moreover, not only in those supplying the retina and optic nerve, but in others which happen to be shown in the tissues outside of the dural sheath of the nerve. The *vena postica*, which has been particularly described by Sachs as giving evidence of an endo- and periphlebitis, could not be identified in any of the sections.

Briefly, then, the changes in this case of central scotoma, which, so far as the history and the perimetric examinations are concerned, seems to belong to the group of the so-called intoxication-amblyopias, are: degeneration of the papillo-macular bundle from the tract, through the chiasm and along the nerve until it reaches the nerve-head; marked thickening of the connective tissue of the affected area, with degeneration of the nerve-fibrils, and hypertrophy of the walls of vessels, associated with a moderate increase in nuclei within the fasciculi; some narrowing of the temporal nerve-fibre layer in the neighborhood of the papilla, and in the same region imperfections in the processes of the ganglion-cells, which, however, in the macular zone are of normal construction.

With reference to the pathological process present in the optic nerve in cases of this description, there is some difference of opinion, and, as has been well stated, "the descriptions of the optic nerves in the recorded cases agree quite as well with an inflammation of the connective tissue of the nerve causing secondary atrophy of the nerve-fibres as with a primary atrophy of the latter associated with secondary interstitial changes following in its track." The same doubt obtains in the present instance, although taking into consideration the marked thickening of the interfascicular septa, the vascular changes and the increase in the nuclei, both upon the edge of the degenerated area and within the fasciculi, even if this increase in nuclei cannot be said to be a marked one, the appearances correspond closely with those usually assigned to an interstitial sclerosing inflammation, which Samelsohn compared with the same pathologic process visible in interstitial hepatitis.

As my specimens show extensive typical tract-atrophy far advanced, and the retinal sections from the same case only a moderate thinning of the nerve-fibre layer on the affected side, without any special change in the ganglion-cells, which, indeed, in the macular zone appear practically unaltered, it is difficult to assume that these cells should be regarded as the starting-point of this affection. In other words, this case fails to confirm the recent contention of Nuel,[1] that central toxic scotoma is not primarily a neuritis of the macular bundles, but a disease of the macular lutea causing degeneration of its cells, and that the optic-nerve changes

[1] Archives d'Ophtalmologie, October, 1895; March and August, 1896. The macular origin of central scotoma was advocated more than twenty years ago by Schoen, and later by Bayer and Treitel, who believed that it indicated a functional weakness of the centre of the retina due to toxic agents.

are secondary to the destruction of the nerve-cells of the macula. To be sure, there is no manner of doubt that macular-fibre degeneration will follow experimentally produced retinal lesions, as has been shown in the excellent research of Usher and Dean,[1] and clinically we know that atrophy of the tissue of the macula lutea, for example, in atrophic central retino-choroiditis, or in so-called macular coloboma, will cause quadrant-atrophy of the optic disk, precisely as this is seen in cases of intoxication-amblyopia If a specimen of this character were submitted to microscopic examination, I have no doubt atrophy of the papillo-macular bundle would be found precisely as it appears in the present instance.

Ophthalmoscopic changes in the macula have been described in cases of toxic amblyopia by Nettleship, Hill-Griffith, and myself; although we did not attribute them to the influence of a toxic agent, but regarded them as coincidences. Macular changes have also been described by Nuel and W. G. Laws, but they are quite as indefinite as those previously recorded.

Nuel has experimentally produced optic-nerve degeneration by administering extract of male fern, and thinks that this disease attacks first the nerve-cells of the retina, and that their destruction brings about the degeneration of the fibres of the optic nerve. Moreover, this degeneration occurs without the intervention of a neuritis. Recently the same author,[2] in a discussion on sympathetic amblyopia, refers to this subject (I quote W. G. Sym's abstract of his paper) as follows: "In a certain number of cases of filix mas amblyopia in dogs there is a distinct degree of neuritis, or at least of blurring of the papilla; but, microscopically, there is no trace of an interstitial neuritis, only an œdema of the nerve-head. This interstitial œdema is consecutive to the destruction of the nerve-fibres, and real neuritis, if it occurs, comes on later, but is neither interstitial nor retrobulbar. Many cases of toxic amblyopia are of this nature; they are instances of parenchymatous neuritis." In my own experiments in quinine-amblyopia[3] the extensive degeneration of the whole visual tract which followed the administration of this drug occurred without preceding neuritis.[4] It was essentially a degenerative process, but, as an examination of my specimens will show, there were no changes in the ganglion-cells of the retina. Therefore, while there may be a retinal origin of degeneration of the papillo-macular bundle, or, indeed, of more extensive disease of the entire nerve, it evidently is not

[1] Trans. of the Ophth. Soc. of the U. K., 1896, vol. xvi. p. 248.

[2] Archives d'Ophtalmologie, March, 1897.

[3] The Toxic Amblyopias; their Classification, Symptoms, and Pathology. Philadelphia, Lea Bros. & Co., 1896, pp. 193–198.

[4] In my earlier experiments in quinine-amaurosis (Trans. Coll. of Phys. of Phila., 1890) I found in many sections, in the earlier stages of the blindness, "that the trabeculæ were less marked and the individual fibrils spread apart, as if the tissue was œdematous and swollen" This observation is similar to the one made by Nuel in dogs suffering from the amblyopia of male fern.

the usual or constant starting-point of this lesion in so-called intoxication-amblyopias. Certainly, degeneration of the ganglion-cells could not have been the cause of the atrophy of the macular fascicle in the present case, nor in several others which have been reported, notably those of Sachs, who, like myself, carefully examined the ganglion-cells of the macula and found them normal. Neither can disease of these cells be held responsible for the atrophy of the optic nerve which occurs in quinine-toxæmia, if I may judge from the examination of a large series of sections in which no notable changes in the ganglion-cells can be demonstrated.

In quinine and salicylic-acid amblyopia, and as I expected I would find in filix mas amblyopia, but I was not successful in securing atrophy, the primary changes are vascular, sometimes, in the earlier stages, of the nature of a pure ischæmia, and later, if the influence of the poison continues, these functional vascular changes, if I may so express myself, become organic ones. Endovasculitis, thickening of the vessel-walls, etc., appear, associated with degeneration and atrophy of the nervous tracts which they supply.

Sometimes a single tract is attacked, as in the tobacco and alcohol-amblyopias, and, again, an entire nerve, as in quinine-amaurosis. Why certain tracts or areas are affected to the exclusion of others, we do not know. Perhaps the process depends upon nutritional disturbances similar to those which occur in certain tracts of the cord in pernicious anæmia, and which subsequently develop into atrophies resembling those seen in locomotor ataxia.

The belief of Sachs, that the earlier stages of these intoxication-amblyopias must be sought for in vascular disturbances, has a good deal to recommend it, and seems borne out by the action of other toxic agents. What exactly is the active principle which produces these nutritional disturbances we do not know. Sometimes it is tobacco, sometimes tobacco and alcohol combined, sometimes it is other poisons, as opium, hashish, iodoform, etc., and sometimes it is a toxin, as, for example, the toxin of diabetes. I have long ago contended that I did not believe it was tobacco alone, or its active principle, nicotine, which was the essential poisonous agent, but that one or more of the many principles freely present in tobacco-smoke, or some toxic influence which they liberate in the system, must be held accountable for the disease. Sachs contends that even in the tobacco cases certain complex chemical combinations occur in the stomach, and there is a resulting transformation of the normal gastric juices into acids of the fatty type which combine with nicotine to form substances which are more injurious than the simple tobacco-bases themselves. Experimental work now being carried on in Chicago under the direction of Dr. Casey Wood indicates that certain stomachic toxins are capable of causing in animals blindness, probably of the type under consideration.